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An approach for the enantioselective synthesis of biologically active furanones from a Morita–Baylis–Hillman adduct

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ABSTRACT

Herein, we disclose an approach for the asymmetric synthesis of both enantiomers of an anti-inflammatory furanone. The approach is based on the utilization of a Morita–Baylis–Hillman adduct as starting material and has as key step a selective epoxide-opening/benzylic oxidation mediated by Palladium (II). This sequence afforded an advanced intermediate, which was used to accomplish the total synthesis. Experimental evidences allowed us to suggest a mechanistic proposal for the oxidation Palladium(II)-mediated.

1. Introduction

The inflammatory process is a sophisticated and complex sequence of events triggered by the human body to fight injuries. It is directly associated with several diseases, such as asthma, cancer, immunological response, and degenerative processes (arthritis and arthrosis).[1]

Some years ago, a new isoform of the cyclooxygenase enzyme, namely COX-2 was discovered and isolated.[2] As a result this new enzyme has been identified as target for the development of new and safer anti-inflammatory drugs. This inducible isoform appears to play a major role in the inflammatory process through the production of prostaglandins.[3] Two selective inhibitors, Vioxx® and Celebra® have been successively launched into the market (Fig. 1).[4,5] However, clinical phase IV assays have demonstrated that Vioxx® increases significantly the risk of cardiovascular issues in patients taking a daily dose.[6] Vioxx® has been voluntary withdrawn from the market in 2004.

Most recently, COX-2 was identified as a target for the development of new compounds to treat some types of cancer[7] and neurodegenerative diseases like Alzheimer[8] and Parkinson.[9]

In a structure–activity relationship study, Leblanc et al.[10] found some furanones as promising anti-inflammatory agents. Among the furanones tested those derived from 5,5-dimethyl-3-(2-propoxy)-4-methanesulfonylphenyl-2(5*H*)-furanone (DFP), showed the best activity (Fig. 1).

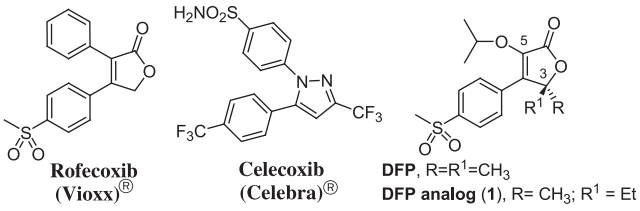

Figure 1. COX-2 selective inhitors and anti-inflammatory furanones.

Substituents at C3 and C5 and particularly isoproxy at C5 were found to improve the pharmacokinetic profile of this type of compounds (Fig. 1).[11]

Thus, we became interested in the total synthesis of new anti-inflammatory agents exhibiting the furanone motif. There are two reports describing the total synthesis of **1**.[11,12] However they are limited on the possible substitution patterns on aromatic ring.

The Morita–Baylis–Hillman (MBH) is known to be a green atom-efficient chemical transformation[13,14] producing multifunctionalized adducts, which are versatile synthons for the preparation of natural products and drugs.[15]

In this paper we describe a new approach for the synthesis of **1** through a Morita–Baylis–Hillman adduct. Furthermore, we disclose a mechanistic proposal to explain our results concerning the

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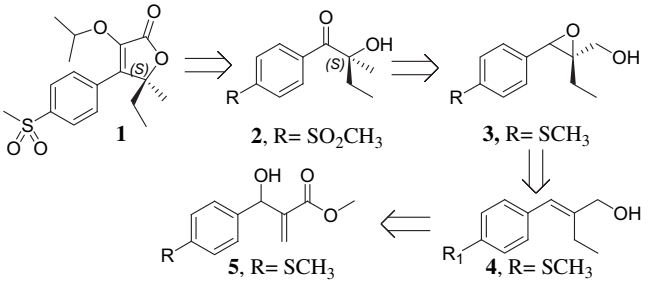
consecutive epoxide opening followed by a Palladium(II)-mediated benzylic oxidation.

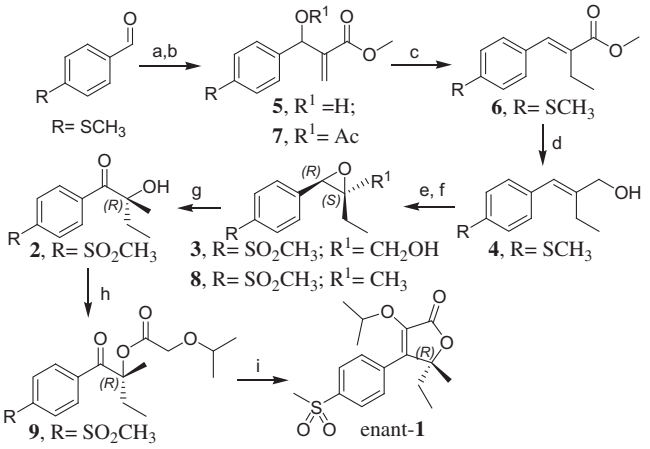
2. Results and discussion

We envisioned the asymmetric synthesis of **1** to be accomplished by esterification of chiral keto-alcohol **2** with isopropoxy acetic acid, followed by a Knoevenagel condensation to form the lactone. Keto-alcohol **2** in turn can be synthesized from chiral epoxide **3**, through a regioselective opening/benzylic oxidation sequence. Asymmetric Sharpless epoxidation with allylic alcohol **4** should provide **3**, which could be prepared from its corresponding Morita–Baylis–Hillman adduct (Scheme 1).



Scheme 1. Retrosynthetic analysis toward the synthesis of DFP analog **1**.

Utilizing our previously reported process the MBH adduct **5** was prepared from thioanisaldehyde in 79% yield.[16,17] Acetylation followed by treatment of the resulting allylic ester with lithium dimethylcopper in ether furnished the cinnamate derivative **6**.[18] α, β-Unsaturated methyl ester was then reduced with DIBAL-H, to afford allylic alcohol **4**, in 37% overall yield after three steps (Scheme 2).



Scheme 2. Synthesis of enantiomeric **1**. Reagents and conditions: a. Methyl acrylate, DABCO, ultrasound, 48 h, 79%; b. AcCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 12 h, 88%; c. CH_3Li, CuI, −20 to −40 °C, 10 h, 60%. d. DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 89%; e. (−)-DIPT, Ti(O^iPr)$_4$, TBHP, CH_2Cl_2, −40 to −20 °C, 70%, 76% ee f. (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (ii) $LiAlH_4$, THF, 0 °C, 30 min, 70% (for two steps); g. 20 mol % $Pd(OAc)_2$, bathocuproine (20 mol %), H_2O, O_2, 100 °C, 30 h, 55%; h. DPC, DMAP, 2-isopropoxy acetic acid, DCE, 70%; i. $CF_3CO_2{}^iPr$, DBU, CH_3CN, reflux, 10 h, 85%.

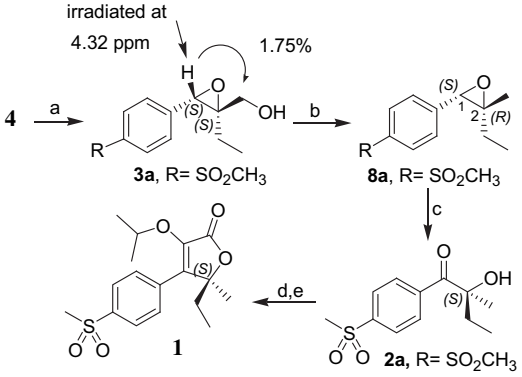
Allylic alcohol **4** was then treated with (*D*)-diisopropyl tartrate at low temperature to give epoxide **3**, in 70% yield and 76% ee. As expected, the thioether moiety was also oxidized to the sulfone in this step. Several modifications (temperature, equivalents of tartrate, etc.) were tested in order to improve enantioselectivity, however we did not succeed.[19] To improve the enantioselectivity of this transformation we also employed Shi's chiral dioxirane, resulting in both lower yield and the enantiomeric excess.[20]

Recently interest in Palladium(II)-catalyzed oxidation reaction with molecular oxygen has increased exponentially. This amazing method, which embraces the also known palladium oxidase catalysis, allows the preparation of carbonyl compounds and diols[21] from alcohols and epoxides and the formation of new C–C and C–N single bonds from alkenes in good yields and under mild experimental conditions.[22]

Despite these developments, the palladium(II)-mediated oxidation of epoxides directly to acyloins has been barely available in literature. To our knowledge the only report was described by Sommerlade and Richter some years ago.[23] This result inspired us to test this method to open chiral epoxide **3** and subsequently oxidize the benzylic position. Thus, after reduction of the primary alcohol function of **3** to the corresponding methyl group by conventional transformations, the resulting epoxide **8** was treated with Palladium (II) acetate in the presence of water, O_2, and bathocuproine to give acyloin **2**, as sole compound in 55% yield (Scheme 2). The synthesis of **1** was then completed by esterification of **2** with 2-isoproxy acetic acid[24] in the presence of DPC and DMAP to give ketoester **9** in 70%, followed by treatment of **9** with isopropyl trifluoroacetate and DBU in refluxing acetonitrile, providing the desired anti-inflammatory agent **1**. All spectroscopic data are in complete agreement to those described in literature. However $[\alpha]_D$ value had the same magnitude, but opposite rotation. The measured $[\alpha]_D$ value for our synthetic compound was +17.2 (*c* 1.02, MeOH) while that described for the *S* isomer was −19 (*c* 1.02, MeOH).[12]

This result was disappointing, because in a undefined point of our strategy a configurational inversion had occurred. Trying to understand it, we have carefully evaluated the whole synthetic strategy. At first glance, two steps could be responsible for this inversion. It is very unlikely that a configurational inversion had occurred during esterification reaction and Knoevenagel condensation steps. So, the inversion should have occurred either during the Sharpless asymmetric epoxidation or during the palladium-mediated opening of the epoxide.

Sharpless epoxidation is a well established methodology and based on its stereochemical rationalization we can assume no inversion had occurred at this step. Despite these considerations, we did the Sharpless reaction again, but using L-(+)-DIPT (71% yield, 80% ee, confirmed by HPLC, Scheme 3).[19] The obtained epoxide **3a** was then investigated by NOE experiment in order to confirm its stereochemistry. The singlet resonance at 4.32 ppm (benzylic hydrogen) was initially irradiated. We observed a net increment of 1.75% on the methylene absorption centered at 3.90 ppm, and thus confirming the *syn* relative stereochemistry of the asymmetric centers. As expected, the accepted model works nicely and no inversion had occurred.



Scheme 3. Reagents and conditions: a. L-(+)-DIPT, Ti(O^iPr)$_4$, TBHP, CH_2Cl_2, −40 to −20 C, 71%, 80% ee b. (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (ii) $LiAlH_4$, THF, 0 °C, 30 min, 70% (for two steps); c. 20 mol % $Pd(OAc)_2$, bathocuproine (20 mol %), H_2O, O_2, 100 °C, 30 h, 55%; d. DPC, DMAP, 2-isopropoxy acetic acid, DCE, 70%; e. $CF_3CO_2{}^iPr$, DBU, CH_3CN, reflux, 10 h, 85%.

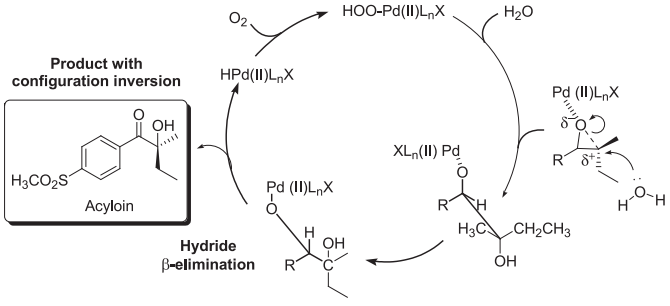
Now we turn our attention to the palladium mediated epoxide ring opening and benzylic oxidation step. A careful inspection shows that the epoxide opening can occur either at the benzylic or at homobenzylic position (C_1 and C_2, respectively, see Scheme 3).

Attack at the homobenzylic position of **8a** (C_2) would form a product in which the configuration of the new stereogenic center would be inverted. On the other hand, attack at C_1 would result in retention of configuration at C_2.[15e] However, C_2 is quaternary center and from a steric point of view, it is most likely to be more difficult to be attacked by a nucleophile than C_1. The presence of a strong electron-withdrawing group at the *para* position of the aromatic ring could compromise C_1, if a positive charge (formal or transient) is formed during the ring opening process. Apparently, the latter effect seems to overweigh steric arguments in this case and explains the observed inversion of configuration. Based on these considerations we restarted the synthetic sequence. Allylic alcohol **4** underwent the Sharpless asymmetric epoxidation to afford **3a**.

Treatment of **8a** with Palladium(II) acetate, molecular oxygen (O_2), and bathocuproine afforded acyloin **2a**, which was esterified and cyclized as before to lead to the chiral lactone **1**, which was purified by column chromatography and recrystallized twice from ethyl acetate/hexane (30:70).

To our delight all spectroscopic and physical data were identical to those reported in literature. The observed $[\alpha]_D$ value for this compound was −17.4 (*c* 1.02, MeOH). The specific rotation described in literature for this compound was $[\alpha]_D$ −19 (*c* 1.02, MeOH). After two recrystallizations the enantiomeric purity was increased to 94% ee.

This evidence confirm the hypothesis that inversion of configuration at C_2 occurs in the epoxide opening. The electronic influence exerted by the SO_2CH_3 group seems to be pivotal in the opening process. Based on these experimental data we have proposed a mechanism to explain the palladium(II)-catalyzed oxidation with molecular oxygen (Scheme 4).



Scheme 4. Mechanistic proposal for the epoxide opening and benzylic oxidation Palladium(II)-mediated.

In the first step, palladium coordinates the oxygen promoting nucleophilic attack by water. β-Elimination hydride delivers the oxidized product and palladium hydride, which after re-oxidation in the presence of O_2, restarts the catalytic cycle (Scheme 4).

3. Conclusion

In summary, we have developed a new strategy, which allows the syntheses of both enantiomers of the anti-inflammatory agent DFP analog **1**. The syntheses were accomplished in 10 steps, in 6% overall yield, from commercially available thioanisaldehyde. This approach demonstrates the synthetic utility of the Morita–Baylis–Hillman and the palladium-(II)/O_2 oxidation reactions.

Further studies are ongoing in our laboratory in order to demonstrate the generality of this synthetic strategy and will be published in due time.

4. Experimental section

4.1. General

The ^1H and ^{13}C spectra were recorded on a Brucker at 250 MHz and 62.5 MHz, respectively. The ^1H and ^{13}C spectra were also recorded on an Inova instrument at 500 MHz and 125 MHz, respectively. The high resolution mass spectra were recorded using a Q-TOF Micromass equipment (Waters, UK). Manipulations and reactions were not performed under dry atmospheres or employing dry solvents, unless otherwise specified. In those cases CH_2Cl_2, DMF, and triethylamine were dried over CaH_2 and distilled. Purification and separations by column chromatography were performed on silica gel, using normal or flash chromatography. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All the reactions, the Morita–Baylis–Hillman reactions were sonicated in an ultrasonic cleaner (81 W, 40 MHz).

*4.1.1. Preparation of (±)-methyl 2-{hydroxy[4-(methylsulfanyl)phenyl]methyl}acrylate (**5**).* A mixture of 4-thiomethylbenzaldehyde (4.0 g, 26.3 mmol), methyl acrylate (11.3 g, 131.5 mmol), and DABCO (1.9 g, 17.1 mmol) in acetonitrile (10 mL) was sonicated in an ultrasound bath for 48 h. Next, excess methyl acrylate and acetonitrile was removed under vacuum. The crude residue was diluted in ethyl acetate (25 mL) and washed with distilled water (15 mL), brine (2×15 mL) then dried over anhydrous Na_2SO_4 and the solvent removed under vacuum. The residue was purified by flash silica gel column chromatography (ethyl acetate/hexanes—30:70) to provide 4.95 g of the MBH adduct **5**, as a white solid. Yield 79%, white solid. Mp: 60–62 °C; IR (film, ν_{max}): 3456, 1712, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ ppm: 7.46 (m, 2H), 7.39 (m, 2H), 6.50 (s, 1H), 6.04 (s, 1H), 5.68 (s, 1H), 3.89 (s, 3H), 3.23 (s, 1H, OH), 2.65 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ ppm: 166.5, 141.8, 138.1, 137.9, 127.0, 126.8, 126.4, 125.7, 72.5, 51.8, 15.6; HRMS (ESI-TOF) calcd for $C_{12}H_{14}O_3S$ $[M+Na]^+$: 261.0562. Found: 261.0537.

*4.1.2. Preparation of (±)-methyl 2-{(acetyloxy)[4-(methylsulfanyl) phenyl]methyl}acrylate (**7**).* To a solution of MBH adduct **5** (1.5 g, 6.3 mmol) in a mixture of dry dichloromethane (30 mL) and dry Et_3N (1.2 mL, 8.2 mmol), under an argon atmosphere, was added a catalytic amount of DMAP. The resulting solution was cooled to 0 °C and then acetyl chloride (0.64 g, 0.7 mL, 8.2 mmol) was slowly added. The reaction was stirred for 12 h and upon completion, the solvent was removed under vacuum. The crude residue was diluted with ethyl acetate (30 mL) and the organic layer washed with water (20 mL), brine (2×20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash silica gel column chromatography (ethyl acetate/hexanes—25:75) to provide 1.55 g of the acylated MBH adduct 7. Yield 88%, light yellow oil; IR (film, ν_{max}): 2950, 1736, 1437, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ ppm: 7.35 (m, 2H), 7.26 (m, 2H), 6.69 (s, 1H), 6.44 (s, 1H), 5.94 (s, 1H), 3.75 (s, 3H), 2.50 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ ppm: 169.1, 165.1, 139.3, 138.8, 134.3, 128.0, 126.1, 125.3, 72.6, 51.8, 20.9, 15.3; HRMS (ESI-TOF) calcd for $C_{14}H_{16}O_4S$ $[M+Na]^+$: 303.0667. Found: 303.0726.

*4.1.3. Preparation of methyl (2E)-2-[4-(methylsulfanyl)benzylidene] butanoate (**6**).* A freshly prepared solution of **7** (0.6 g, 2.1 mmol) in dry diethyl ether (50 mL) was kept under stirring at −40 °C. In another flask, a suspension of CuI (0.48 g, 2.5 mmol) in dry ethyl ether (10 mL) was prepared. The resulting suspension was stirred and then cooled to 0 °C and then a 1.6 mol L^{-1} solution of methyllithium (0.112 g, 3.2 mL) was slowly added. The resulting solution was stirred for 10 min at 0 °C and immediately after it was cooled to −40 °C and transferred via cannula to the solution of **7** at −40 °C. The yellow mixture was stirred for 8 h at −40 °C. The medium was diluted with

ethyl ether (20 mL) and a solution of NH_4Cl/NH_4OH 1:1 (5 mL) was added. The mixture was stirred until an intense blue coloration had appeared. The organic layer was washed with water (10 mL), brine (2×15 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash silica gel column chromatography (ethyl acetate/hexanes—20:80) to afford 0.3 g of olefin **6**, as a sole isomer. Yield 60%, light yellow oil; IR (film, ν_{max}): 2966, 1708, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ ppm: 7.59 (s, 1H), 7.31 (m, 2H), 7.25 (m, 2H), 3.82 (s, 3H), 2.56 (q, J=7.5 Hz, 2H), 2.51 (s, 3H), 1.18 (t, J=7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ ppm: 168.7, 139.3, 137.9, 134.0, 132.2, 129.6, 125.9, 51.9, 20.9, 15.5, 13.8; HRMS (ESI-TOF) calcd for $C_{13}H_{16}O_2S$ $[M+H]^+$: 237.0949. Found: 237.0918.

*4.1.4. Preparation of (2E)-2-[4-(methylsulfanyl)benzylidene]butan-1-ol (**4**).* To a solution of cinnamate ester **6** (0.4 g, 1.7 mmol) in dry dichloromethane (12 mL), at −78 °C under an inert gas atmosphere, was added, a 1.5 mol L^{-1} solution of DIBAL-H in hexane (2.5 equiv, 2.8 mL). The reaction was stirred for 2 h at −78 °C and then methanol (six drops) was added. The mixture was warmed to 0 °C followed by the addition of 10 mL of a saturated solution of sodium acetate. The mixture was stirred until the formation of a gel, which was filtered on pad of Celite. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product shows a purity grade high enough to be used in the next step without additional purification. Yield 89% (0.32 g), light yellow oil; IR (film, ν_{max}): 3350, 2962, 1491, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ ppm: 7.30 (m, 2H), 7.26 (m, 2H), 6.52 (s, 1H), 4.30 (d, J=0.8 Hz, 2H), 2.56 (s, 3H), 2.40 (q, J=6.0 Hz, 2H), 1.91 (s, 1H, OH), 1.19 (t, J=6.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ ppm: 143.2, 136.4, 134.3, 128.9, 126.4, 124.3, 66.7, 21.9, 16.0, 13.1; HRMS (ESI-TOF) calcd for $C_{12}H_{16}OS$ $[M+Na]^+$: 231.0820. Found: 231.0781.

*4.1.5. Preparation of {2-ethyl-3-[4-(methylsulfonyl)phenyl]oxiran-2-yl}methanol (**3**). rac-**3**:* To a stirred solution of allylic alcohol **4** (0.1 g, 0.48 mmol) in dichloromethane (15 mL), at 0 °C, was added, *m*-chloroperbenzoic acid 70% (4.0 equiv, 0. 47 g, 1.92 mmol). The resulting mixture was stirred for 12 h at room temperature and upon completion, the reaction was quenched with a saturated solution of sodium bisulfite (8 mL). The mixture was diluted with dichloromethane (15 mL) and the phases were separated. The aqueous layer was washed with dichloromethane (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash silica gel column chromatography (ethyl acetate/hexanes—80:20) to give 0.104 g of racemic epoxide **3**, as a viscous oil, in 90% yield.

Chiral **3** (*S,S*) *and* (*R,R*): To a stirred suspension of 4 Å molecular sieves (60 mg) in dry dichloromethane (1.0 mL), at −40 °C, under an inert gas atmosphere, was added a solution of titanium *tetra*-isopropoxide (73 μL, 0.27 mmol) and (+)-diisopropyl tartrate (36 μL, 0.17 mmol) dissolved in dry CH_2Cl_2 (1.0 mL). The mixture was stirred for 1 h. Next, a 5 mol L^{-1} solution *tert*-butyl-hydroperoxide in nonane (0.32 mL, 1.6 mmol) was added. After 15 min. of stirring, a solution of allylic alcohol **4** (0.05 g, 0.24 mmol) in dry dichloromethane (3,0 mL) was cannulated to the reaction mixture. The final mixture was warmed to −20 °C and stirred for 30 h. After that time, the reaction mixture was warmed to 0 °C and diluted with dichloromethane (10 mL) and distilled water (5 mL). The stirred mixture was slowly warmed to room temperature and then a 10% solution of NaOH was added (2.0 mL). The mixture was filtered over a pad of Celite and the cake was washed with dichloromethane (15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash silica gel column chromatography (ethyl acetate/hexanes—80:20) as the eluent to provide epoxide (*S,S*)-**3a** (43 mg), as a viscous oil, in 71% yield and 90:10 er. The same procedure was used to prepare enantiomeric epoxide **3**, however (−)-diisopropyl tartrate was used instead. Epoxide (*R,R*)-**3** (42 mg) was obtained as a viscous oil, in 70% yield and 88:12 er. The enantiomeric purity of both epoxide was determined by HPLC.

(*S,S*)-**3a** $[\alpha]_D^{25}$ +16.0 (*c* 1.2, MeOH); for the enantiomer (*R, R*)-**3** $[\alpha]_D^{25}$ −15.0 (*c* 1.2, MeOH); IR (film, ν_{max}): 3432, 2970, 2921, 1299, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ ppm: 7.94 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 4.32 (s, 1H), 3.90 (q, 2H), 3.08 (s, 3H), 1.80 (br s, 1H), 1.40 (m, 2H), 0.82 (t, J=7.8 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ ppm: 142.2, 139.6, 127.3, 127.1, 67.3, 62.1, 59.5, 44.5, 20.8, 8.98; HRMS (ESI-TOF) calcd for $C_{12}H_{16}O_4S$ $[M+Na]^+$: 279.0667. Found: 279.0732.

*4.1.6. Preparation of (S,R)-2-ethyl-2-methyl-3-[4-(methylsulfonyl) phenyl]oxirane (**8a**).* To a solution of epoxide **3a** (0.106 g, 0.41 mmol) in dry dichloromethane (12 mL), at 0 °C and under argon atmosphere, was added triethylamine (77 μL, 0.53 mmol) and mesyl chloride (38 μL, 0.53 mmol). After stirring for 10 min, distilled water (8 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3×20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was used for the next step without purification.

(*S,S*)-{2-ethyl-3-[4-(methylsulfonyl)phenyl]oxiran-2-yl}methyl methanesulfonate. Yield >99% (0.13 g), viscous tinged yellow oil; IR (film, ν_{max}): 3000, 1351, 1295, 1171, 1148, 958, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ ppm: 7.96 (d, J=7.8 Hz, 2H), 7.54 (d, J=7.8 Hz, 2H), 4.43 (q, 2H), 4.23 (s, 1H), 3.14 (s, 3H), 3.09 (s, 3H), 1.42 (m, 2H), 0.90 (t, J=7.8 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ ppm: 140.7, 140.0, 127.4, 127.3, 69.8, 64.4, 61.2, 44.5, 38.0, 20.3, 8.79.

A solution of the above mesylate (0.103 g, 0.32 mmol) in dry THF, at 0 °C, under an argon atmosphere, was added to a stirred suspension of $LiAlH_4$ (0.06 g, 1.55 mmol) in dry THF (5 mL). The reaction was stirred for 30 min. Then, a 10% solution of NaOH (1.0 mL) was slowly added at 0 °C. [*Caution*: *A very exothermic and vigorous reaction occurs during this addition and should therefore be carefully controlled*]. The resulting mixture was slowly warmed to room temperature and stirred until formation of a white solid. The mixture was filtered on a pad of Celite and the cake was washed with ethyl acetate (3×20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (ethyl acetate/hexanes—50:50) to provide 50 mg of epoxide **8a**, as a viscous colorless oil, in 70% yield for two steps. (*S,R*)-**3a**: $[\alpha]_D^{25}$ +11.0 (*c* 1.0, MeOH); for the enantiomer (*R,S*)-**3**: $[\alpha]_D^{25}$ −10.0 (*c* 1.0, MeOH); IR (film, ν_{max}): 2974, 1308, 1149 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), δ ppm: 7.93 (d, J=8.7 Hz, 2H), 7.52 (d, J=8.7 Hz, 2H), 3.94 (s, 1H), 3.05 (s, 3H), 1.49 (s, 3H), 1.30 (m, 2H), 0.84 (t, J=7.8 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$), δ ppm: 143.0, 139.4, 127.4, 127.1, 65.1, 64.0, 44.5, 24.6, 21.4, 9.16; HRMS (ESI-TOF) calcd for $C_{12}H_{16}O_3S$ $[M+H]^+$: 241.0898. Found: 241.0901.

*4.1.7. Preparation of (S)-2-hydroxy-2-methyl-1-[4-(methylsulfonyl) phenyl]butan-1-one (**2a**).* A mixture of palladium acetate (0.0041 g, 20 mol %) and bathocuproine (0.0067 g, 20 mol %) in distilled water (3.0 mL) was stirred for 24 h. To this final mixture, epoxide **3a** (0.018 g, 0.075 mmol) was added and the reaction was warmed to 100 °C, under an oxygen atmosphere. The reaction was stirred for 30 h at 100 °C. Then the mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The organic layer was washed with water (5 mL), brine (2×5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (ethyl acetate/hexanes—55:45) to provide 10 mg of hydroxyketone **2a**, as a viscous oil, in 55% yield. (*S*)-**2a**: $[\alpha]_D^{25}$ −18.0 (*c* 1.0, MeOH); for the enantiomer

(*R*)-**2**: $[\alpha]_D^{25}$ +17.0 (*c* 1.0, MeOH); IR (film, ν_{max}): 3493, 2970, 2929, 1683, 1307, 1148 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), δ ppm: 8.15 (m, 2H), 8.04 (m, 2H), 3.08 (s, 3H), 1.93 (m, 2H), 1.59 (s, 3H), 0.88 (t, *J*=6.2 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$), δ ppm: 204.3, 143.7, 139.4, 130.0, 127.5, 80.0, 44.3, 33.7, 26.4, 7.86; HRMS (ESI-TOF) calcd for $C_{12}H_{16}O_4S$ $[M+Na]^+$: 279.0667. Found: 279.0656.

*4.1.8. (S)-2-Methyl-1-[4-(methylsulfonyl)phenyl]-1-oxobutan-2-yl (propan-2-yloxy)acetate (**9a**).* To a mixture of isopropyl acetic acid (5.3 mg, 0.045 mmol) and a catalytic amount of DMAP in dichloroethane (3.0 mL), at 0 °C, was added α-hydroxyketone **2a** (8.0 mg, 0.03 mmol) and then diisopropyl carbodiimide (5.7 mg, 0.045 mmol) during 3 h. The resulting mixture was stirred for 10 h at room temperature and then the excess of dichloroethane was removed under vacuum. The crude residue was diluted with ethyl acetate (10 mL) and the organic layer was washed with water (10 mL), brine (2×5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash silica gel column chromatography (ethyl acetate/hexanes—55:45) to provide the ester **53** (8.0 mg, 0.022 mmol) as a white solid in a 70% yield. (*S*)-**9a**: $[\alpha]_D^{25}$ −19.0 (*c* 1.0, MeOH); lit. $[\alpha]_D^{25}$ −19.3 (*c* 1.0, MeOH); for the enantiomer (*R*)-**9**: $[\alpha]_D^{25}$ +18.8 (*c* 1.0, MeOH); ^1H NMR (250 MHz, $CDCl_3$), δ ppm: 8.15 (m, 2H), 7.99 (m, 2H), 3.99 (d, *J*=2.5 Hz, 2H), 3.46 (hept, *J*=6.0 Hz, 1H), 3.07 (s, 3H), 2.27 (m, 1H), 2.05 (m, 1H), 1.72 (s, 3H), 1.11 (two d, 6H), 1.00 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$), δ ppm: 197.9, 170.1, 143.4, 139.4, 129.2, 127.5, 87.5, 72.8, 65.8, 44.3, 30.6, 21.7, 21.6, 21.2, 7.6; HRMS (ESI-TOF) calcd for $C_{17}H_{24}O_6S$ $[M+Na]^+$: 379.1191. Found: 379.1032.

*4.1.9. (S)-5-Ethyl-3-isopropoxy-5-methyl-4-[4-(methylsulfonyl)phenyl]furan-2(5H)-one (**1**).* To a solution of ester (*S*)-**9a** (0.005 g, 0.014 mmol) in dry and degassed CH_3CN (1.5 mL) was added *i*-PrOOCCF$_3$ (2.5 μL, 0.017 mmol) and DBU (3.2 μL, 0.021 mmol). The mixture was refluxed for 10 h. Then, the reaction medium was cooled to room temperature and neutralized with a 1 mol L^{-1} solution of HCl (six drops). The solvent was removed under vacuum. The crude product was diluted with distilled water (3 mL) and the aqueous phase was extracted with ethyl acetate (3×4 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash silica gel column chromatography (ethyl acetate/hexanes—50:50) and recrystallized twice to provide 4 mg of lactone **1**, as a white solid, in 85% yield. (*S*)-**1**: $[\alpha]_D^{25}$ −17.4 (*c* 1.02, MeOH); lit. $[\alpha]_D^{25}$ −19.0 (*c* 1.02, MeOH); for the enantiomer (*R*)-**1**: $[\alpha]_D^{25}$ +17.2 (*c* 1.02, MeOH); IR (film, ν_{max}): 2978, 2931, 1754, 1152 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), δ ppm: 8.00 (m, 2H), 7.85 (m, 2H), 5.32 (hept, *J*=6.2 Hz, 1H), 3.10 (s, 3H), 2.07 (dq, *J*=14.8, 7.4 Hz, 1H), 1.94 (dq, *J*=14.7, 7.3 Hz, 1H), 1.65 (s, 3H), 1.30 (d, *J*=3.5 Hz, 3H), 1.28 (d, *J*=6.0 Hz, 3H), 0.83 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm: 167.0, 141.6, 140.4, 139.3, 135.9, 128.7, 127.7, 85.9, 73.8, 44.4, 31.5, 25.9, 22.7, 7.6; HRMS (ESI-TOF) calcd for $C_{17}H_{22}O_5S$ $[M+H]^+$: 339.1266. Found: 339.1214.

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Supplementary data

Spectra of all compounds are supplied as Supplementary data. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.077. These data include MOL files and InChIKeys of the most important compounds described in this article.

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